Docket No.: 007841.P001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Terry M. Fredeking et al.

Application No.: 10/038,557

Filed: January 3, 2002

Title: **COMPOSITIONS AND METHODS FOR TREATING HEMORRHAGIC VIRUS INFECTIONS AND OTHER DISORDERS**

Art Group: 1617

Examiner: Yong Soo Chong

APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Board:

Appellant (hereinafter "Appellant") submits one copy of the following Appeal Brief pursuant to 37 C.F.R. § 1.192 for consideration by the Board of Patent Appeals and Interferences. Appellant also submits herewith a check in the amount of $250.00 to cover the cost of filing the opening brief as required by 37 C.F.R. § 41.20(b)(2). Please charge any additional amount due or credit any overpayment to deposit Account No. 02-2666.

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I. REAL PARTY IN INTEREST

Terry M. Fredeking and George M. Ignatyev, the parties named in the caption, assigned their rights to the invention disclosed in the subject application through an Assignment recorded on July 27, 2000, at reel and frame 012667/0902 to Antibody Systems, Inc. Therefore, Antibody Systems, Inc. is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

Claims 13-26 are pending in the application. The Examiner has rejected claims 13-26. Therefore, Appellant appeals the rejection of claims 13-26.

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to the final rejection mailed December 11, 2006. Thus, claims 13-26 stand as presented in the response to Office Action dated August 15, 2006 and filed October 5, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The embodiments of the instant application provide a process comprising contacting blood or a fraction thereof (*in vitro* or *in vivo*) with a therapeutic substance selected from at least one of tetracyclines and tetracycline-like compounds thereby increasing the level of cytokine receptors in the blood or the fraction thereof; and after the contacting, isolating or collecting the blood, the fraction thereof or a portion of the blood having the increased cytokine receptors thereby producing a composition suitable for administration for the treatment of a disease, condition or disorder. (App., p.3, 22-23, ¶¶ [0021], [0296]). Further embodiments of the instant application provide, after the collecting, processing the portion of the blood to isolate a blood fraction comprising cytokine receptors. (App., p.3, 23, ¶¶ [0021], [0297]).

Independent claim 13 recites a process comprising contacting blood or a fraction thereof with a therapeutic substance selected from at least one of tetracyclines and tetracycline-like

compounds thereby increasing the level of cytokine receptors in the blood or the fraction thereof. (App., p.3, 22-23, ¶¶ [0021], [0296]). *In vivo* contacting can include administering one or more tetracycline or tetracycline-like compound(s) to a mammal. (App., p.23, ¶ [0297]). For example, administering one or more tetracycline or tetracycline-like compound(s) to mice can be accomplished intramuscularly or orally. (App., p.34, 40, ¶¶ [0410-0417], [0481]). Additionally, for example, administering one or more tetracycline or tetracycline-like compound(s) to humans can be accomplished orally. (App., p.41, ¶ [0502]). *In vitro* contacting can include, for example, treating white blood cells harvested from the buffy coat of blood with one or more tetracycline or tetracycline-like compound(s). (App., p.23, ¶¶ [0300]-[0301]). Tetracycline compounds can include chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline as well as other chemically-modified tetracyclines. (App., p.11-14, ¶¶ [0163]-[0190]). Tetracycline-like compounds can include thalidomide, aureomycin, sulfa drugs and other compounds that exhibit tetracycline-like activity. (App., p.11, ¶¶ [0161]-[0162]). Contacting the blood or a fraction thereof with at least one of tetracyclines or tetracycline-like compounds induces at least a three-fold increase of cytokine receptors, such as tumor necrosis factor and/or interleukin-1 receptors, from baseline. (App., p.11, 22-23, ¶¶ [0156], [0296]). Independent claim 13 further includes, after the contacting, isolating the blood or fraction thereof containing the increased cytokine receptors, such as by fractionation, in preparation for delivery to treat a disease, condition or disorder. (*Id.*)

Dependent claim 14 depends from independent claim 13 and recites the limitation that the contacting is *in vivo*. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 15 depends from independent claim 13 and recites the limitation that the contacting is *in vitro*. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 16 depends from independent claim 13 and recites the limitation that cytokine receptors are increased at least three-fold relative to non-contacted blood or a fraction thereof. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 17 depends from independent claim 13 and recites the limitation that cytokine receptors are selected from the group consisting of interleukin-1 receptors and tumor necrosis factor receptors. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 18 depends from independent claim 13 and recites the limitation further comprising processing the isolated blood or the fraction thereof by a process selected from the group consisting of: centrifugation, filtration, fractional precipitation, organic solvent precipitation, selective absorption, isoelectric precipitation, and chromatography. (App., pp.23-24, ¶ [0306]).

Dependent claim 19 depends from claim 18 and recites the limitation that the blood or the fraction thereof includes a gamma-globulin fraction, an anti-hemophilia factor fraction, an albumin fraction, serum and plasma. (App., p.23, ¶ [0297]).

Dependent claim 20 depends from independent claim 13 and recites the limitation further comprising administering the composition to treat a disease, condition or disorder wherein the disease, condition or disorder is one of viral hemorrhagic diseases, sepsis, cachexia, rheumatoid arthritis, acute cardiovascular events, chronic myelogenous leukemia, transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis, systemic inflammatory response syndrome, adult respiratory distress syndrome, acute liver failure, inflammatory bowel disease and Crohn's disease. (App., p.2, ¶ [0015]).

Independent claim 21 recites a process comprising contacting blood *in vivo* with a therapeutic substance selected from at least one of tetracyclines and tetracycline-like compounds thereby increasing the level of cytokine receptors in the blood. (App., p.3, 22-23, ¶¶ [0021], [0296]). *In vivo* contacting can include administering one or more tetracycline or tetracycline-like compound(s) to a mammal. (App., p.23, ¶ [0297]). For example, administering one or more tetracycline or tetracycline-like compound(s) to mice can be accomplished intramuscularly or orally. (App., p.34, 40, ¶¶ [0410-0417], [0481]). Additionally, for example, administering one or more tetracycline or tetracycline-like compound(s) to humans can be accomplished orally. (App., p.41, ¶ [0502]). Tetracycline compounds can include chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline as well as other chemically-modified tetracyclines. (App., pp.11-14, ¶¶ [0163]-[0190]). Tetracycline-like compounds can include thalidomide, aureomycin, sulfa drugs and other compounds that exhibit tetracycline-like activity. (App., p.11, ¶¶ [0161]-[0162]). Contacting the blood with at least one of tetracyclines or tetracycline-like compounds induces at least a three-fold increase of cytokine

receptors, such as tumor necrosis factor and/or interleukin-1 receptors, from baseline. (App., p.11, 22-23, ¶¶ [0156], [0296]). Independent claim 21 further includes, after the contacting, a portion of the blood can be collected. (App., p.23, ¶ [0297]). For example, blood samples can be collected from the orbital sinuses of mice. (App., p.40, ¶ [0477]). Additionally, for example, blood samples can be collected from humans intravenously. (App., p.41, ¶ [0502]). Independent claim 21 further includes, after the collecting, processing the portion of the blood to isolate a blood fraction comprising cytokine receptors, such as by fractionation. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 22 depends from independent claim 21 and recites the limitation that processing is selected from the group consisting of: centrifugation, filtration, fractional precipitation, organic solvent precipitation, selective absorption, isoelectric precipitation and chromatography. (App., pp.23-24, ¶ [0306]).

Dependent claim 23 depends from independent claim 21 and recites the limitation that the cytokine receptors are selected from the group consisting of interleukin-1 receptors and tumor necrosis factor receptors. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 24 depends from independent claim 21 and recites the limitation that, prior to the collecting, the number of cytokine receptors in the portion of the blood is increased by a least three-fold relative to the portion of the blood prior to the contacting with the therapeutic substance. (App., p.11, 22-23, ¶¶ [0156], [0296]).

Dependent claim 25 depends from independent claim 21 and recites the limitation that the blood or the fraction thereof includes a gamma-globulin fraction, an anti-hemophilia factor fraction, an albumin fraction, serum and plasma. (App., p.23, ¶ [0297]).

Dependent claim 26 depends from independent claim 21 and recites the limitation further comprising administering the blood or fraction thereof to treat a disease, condition or disorder wherein the disease, condition or disorder is one of viral hemorrhagic diseases, sepsis, cachexia, rheumatoid arthritis, acute cardiovascular events, chronic myelogenous leukemia, transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis, systemic

inflammatory response syndrome, adult respiratory distress syndrome, acute liver failure, inflammatory bowel disease and Crohn's disease. (App., p. 2, ¶ [0015]).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues involved in this Appeal are as follows:

A. Whether claims 13-26 are unpatentable under 35 U.S.C. §103(a) as obvious over U.S. Pat. No. 6,015,804 to Golub et al. ("*Golub*").

All of the claims do not stand or fall together. The basis for the separate patentability of the claims is set forth below.

VII. ARGUMENT

The Examiner rejects claims 13-26 as being unpatentable over *Golub*. Appellant respectfully traverses these rejections for at least the following reasons.

A. Overview of the Prior Art

1. Overview of *Golub*

Golub describes a method of enhancing endogenous interleukin-10 (IL-10) production in mammalian cells and tissues, which includes administering an effective amount of a tetracycline derivative. (Abstract). IL-10 is a 35-40 kDa peptide cytokine. (col. 1, ln. 61). According to *Golub*, IL-10 is known to down-regulate the production and activity of IL-1 and TNF alpha. (col. 8, lns. 60-64). The tetracycline derivative preferably has little or no antimicrobial activity. (col. 7, lns. 35-37). The tetracycline derivative can be administered *in vivo* systemically, orally or topically to a mammal. (col. 8, lns. 14, 23, 27-28). The tetracycline derivative can alternatively be used *in vitro* or *ex vivo* by culturing with cells. (col. 5, ln. 55; cols. 9-12, Exs. 1-5).

Golub does not teach or suggest contacting blood or a fraction thereof with tetracyclines or tetracycline-like compounds to increase cytokine receptors. *Golub* does not teach or suggest that the cytokine receptors are IL-1 receptors or TNF receptors. *Golub* does not teach or suggest that the level of cytokine receptors is increased at least three-fold in the blood or fraction thereof after contact with tetracyclines or tetracycline-like compounds. *Golub* does not teach or suggest

isolating the blood or fraction thereof after contact with tetracyclines or tetracycline-like compounds. *Golub* does not teach or suggest isolating the blood or the fraction thereof by filtration, fractional precipitation, organic solvent precipitation, selective absorption, isoelectric precipitation or chromatography. *Golub* does not teach or suggest that the blood or the fraction thereof includes a gamma-globulin fraction, an anti-hemophilia factor fraction, an albumin fraction, serum or plasma. *Golub* does not teach or suggest that the isolated blood or fraction thereof is a composition suitable for administration for a treatment, disease or condition. *Golub* does not teach or suggest administering the composition to treat a disease, condition or disorder wherein the disease, condition or disorder is one of viral hemorrhagic diseases, sepsis, cachexia, rheumatoid arthritis, acute cardiovascular events, chronic myelogenous leukemia, transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis, systemic inflammatory response syndrome, adult respiratory distress syndrome, acute liver failure, inflammatory bowel disease or Crohn's disease.

B. Rejection of Claims 13-26 Under 35 U.S.C. § 103 as Made Obvious by *Golub*

In order to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (2) there must be a reasonable expectation of success; and (3) the references when combined must teach or suggest all of the claim limitations. MPEP 2142.

Appellant submits that independent claims 13 and 21 are patentable over *Golub* for at least the reasons that (a) the cited reference does not teach or suggest all of the claim limitations in independent claims 13 and 21; (b) there is no motivation to modify the reference to arrive at the inventions embodied in claims 13 and 21; (c) there is no reasonable expectation of success in modifying Golub to arrive at the inventions embodied in claims 13 and 21; and (d) the Examiner has misapplied the tenets of patent law in rejecting claims 13 and 21.

1. Lack of teaching or suggestion of every element in the claims

Independent claim 13 includes the limitation of "***after the contacting***, isolating the blood or fraction thereof having the increased cytokine receptors." (App., claim 13). Independent claim

21 includes the limitation of "***after the contacting***, collecting a portion of the blood [and] . . . processing the portion of the blood to isolate a blood fraction comprising cytokine receptors." (App., claim 21). Representatively, the blood or fraction thereof can be processed by centrifugation or filtration into plasma and serum fractions ***after*** contact with at least one tetracycline or tetracycline-like compound. (App., p.23, ¶¶ [0303]-[0304]). The plasma fraction can be further processed into an albumin-containing fraction, a globulin-containing fraction, an antihemophilic factor-containing fraction and a fraction containing soluble IL-1 receptor or soluble TNF receptor. (App., pp. 23-29, ¶¶ [0305]-[0354]). Generally, these methods comprise one or more of the following procedures: (a) fractional precipitation with ammonium sulfate and similar salts; (b) organic solvent precipitation with cold ethanol or acetone and other such alcohols and ketones; (c) selective adsorption on calcium phosphate gels or with barium sulfate; (d) isoelectric precipitation by pH adjustment to the point at which there is no net charge on a given protein; and (e) chromatography by use of adsorbents such as CM- or DEAE-cellulose or by "Sephadex" gel filtration. Other procedures for selectively fractionating and purifying blood proteins involve the use of amino acids such as glycine and beta alanine, water-soluble organic polymers such as polyethylene glycol and polypropylene glycol, and water-insoluble polyelectrolyte polymers containing basic amino groups such as the dimethylaminopropylimide group. (App., p.24, ¶ [0306]). In sum, the blood or fraction thereof is treated with tetracycline or tetracycline-like compound, ***then*** isolated or collected after cytokine receptors have increased at least three-fold, and ***then*** processed into a composition that can be administered to a patient. (App., p.23, ¶ [0297]).

The isolating of the blood or fraction thereof having the ***increased cytokine receptors after contact*** with at least one of tetracycline or tetracycline-like compound is not taught or suggested by *Golub* for at least the following reasons: (i) *Golub* describes a method for increasing cytokines, specifically IL-10, whereas claims 13 and 21 describe processes for producing a composition which includes cytokine receptors, and (ii) *Golub* relates to ***cytokines*** (not cytokine receptors) whereas claims 13 and 21 describe processes for producing a composition including ***cytokine receptors***. More specifically, *Golub* only describes a method of enhancing endogenous ***cytokine IL-10 production*** in mammalian cells and tissues, which includes administering an effective amount of a tetracycline derivative. (Abstract).

Golub does not teach or suggest a process to produce a composition. Moreover, Golub does not teach or suggest isolating the blood or the fraction thereof having the increased cytokine receptors. While *Golub* describes density gradient centrifugation of blood in Examples 1 through 5, this process is performed ***before*** any administration of a tetracycline derivative with a limitation that the tetracycline derivative preferably has little or no antimicrobial activity. (col. 7, lns. 35-37). Thus, *Golub* does not teach or suggest each and every limitation of claims 13 and 21.

2. Lack of motivation to modify

a) *Golub* teaches away from claims 13 and 21

In addition, there is no motivation in *Golub* to modify the reference to teach claims 13 ands 21. *Golub* is concerned with enhancing the production of the ***cytokine*** IL-10. (col. 5, lns. 43-44). In contrast, claims 13 and 21 are directed to a process, which includes an increase in ***cytokine receptors*** as compared to the endogenous levels of cytokine receptors in a healthy mammal, which decreases the pathological conditions caused by an overproduction of cytokines. (App, p.1, ¶ [0006]). In the Summary of the Invention, for example, Appellant discloses "blood-derived compositions and methods of treating viral hemorrhagic diseases or disorders and other diseases involving a cytotoxic response in which . . . IL-1 . . . [is] elevated." (App., p.3., ¶ [0023]). Thus, Appellants disclose a technique for the ***uptake of excessive cytokine***, while *Golub* is concerned with ***enhancing cytokine production***. Thus, *Golub* actually teaches away from claims 13 and 21. MPEP § 2141.02(VI). Consequently, taking *Golub*, there would not be any reasonable expectation of success in isolating the blood or fraction thereof having the increased cytokine receptors, as disclosed in claims 13 and 21, because *Golub* actually teaches away from claims 13 and 21 in that *Golub* teaches the ***enhancement*** of the cytokine IL-10 rather than the ***uptake*** of excessive cytokines. MPEP § 2143.02. In sum, there is no motivation to modify *Golub* to teach isolating a blood or a fraction thereof having increased cytokine receptors for the uptake of excessive cytokines, as taught in claims 13 and 21, because *Golub* is directed to increasing cytokines.

b) *Golub* does not suggest the desirability of claims 13 and 21

Furthermore, *Golub* does not suggest the desirability of claims 13 and 21. MPEP § 2143.01. Assuming the reference to tetracyclines in *Golub* inherently increases the level of cytokine receptors, it does not follow that *Golub* provides any motivation for isolating blood having the increased cytokine receptors. In other words, if *Golub* does not recognize the inherent properties of tetracycline, namely, that tetracycline increases ***cytokine receptors*** (not the cytokine IL-10), as admitted by the Examiner's argument, *Golub* cannot provide the motivation to isolate the blood with the increase cytokine receptors. (Final Office Action dated December 11, 2006 ("Dec. 11 Final Office Action")). Moreover, the isolation operations cited by the Examiner (examples 1 and 2 in *Golub*) also do not relate to isolation of the blood or fraction thereof for a composition for the treatment of a disease, condition or disorder. (*Id.*) Instead, *Golub* describes culturing peripheral blood monocyte cells (PBMNC) and performing various experiments on the cells. (col. 9, lns. 25-27).

3. <u>No reasonable expectation of success</u>

Additionally, *Golub* does not make obvious claims 13 and 21 because there is no reasonable expectation of success of arriving at Appellant's inventions embodied in claims 13 and 21. MPEP § 2143.02. In the December 11 Final Office Action, the Examiner states "[a] person of ordinary skill in the art would have been motivated to isolate the blood by density gradient centrifugation because of the expectancy to isolate and increase the amount of blood containing increased cytokine receptors to be used for therapeutic means." (Dec. 11 Final Office Action, p.4). *Golub*, however, ***does not contain a single reference with respect to increasing cytokine receptors upon administration of tetracycline or a tetracycline-like compound to blood or a fraction thereof.*** With no mention of this limitation, a limitation included in claims 13 and 21, how can one of ordinary skill in the art have a reasonable expectation of success of modifying *Golub* to arrive at claims 13 and 21?

4. Improper arguments by Examiner

The Examiner's remarks rejecting the claims should be disregarded because the arguments are misplaced and inapplicable with respect to the claims. In the December 11 Final Office Action, the Examiner states, "[p]roducts of identical chemical composition cannot have mutual exclusive properties." (December 11 Final Office Action, p.3). As a preliminary matter, claims 13 and 21 are directed to a process not a product. Further, the Examiner has completely disregarded that *Golub* contemplates ***tetracycline derivatives with little or no antimicrobial activity***. (col. 7, lns. 35-37; claim 2). Appellant's invention does not similarly include such a limitation, but only requires tetracycline or a tetracycline-like compound administered to blood or a fraction thereof. (App., claims 13, 21). Such a dramatic change in the property of a chemical, namely, a change in the level of microbial activity of the compound, would not necessarily result in the same effects when administered to blood. Thus, the Examiner has not met his burden in relying on a theory of inherency because the Examiner has not provided a basis in fact and/or technical reasoning to reasonably support the determination that he allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990); MPEP § 2112(IV). Moreover, obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. MPEP § 2141.02(V).

Moreover, the Examiner's remarks are further inapplicable in that the Examiner mischaracterizes the claims by stating that Appellant is "claiming a biological pathway as the basis for their invention." (Dec. 11 Final Office Action, p.5). Claims 13 and 21, are in fact directed to a process and not simply a biological pathway, as can be noted in the preamble. (App., claims 13, 21). The novel and non-obviousness of the claim lies in the process, not a biological pathway.

Additionally, the Examiner's remarks should further be disregarded in that the Examiner states that the "method steps are already known." (Dec. 11 Final Office Action, p.6). Claims 13 and 21 are directed to contacting blood with tetracycline or a tetracycline-like derivative, then "harvesting" the blood, then processing the blood to be administered to treat certain diseases or conditions. (App., claims 13, 21). These "method steps" are not known and the Examiner has not

referenced any prior art to support his position. (Dec. 11 Final Office Action, p.6). If these "method steps" were indeed "known", then Appellant assumes that the Examiner would have made a rejection under the principle of anticipation (35 U.S.C. § 102) rather than obviousness (35 U.S.C. § 103), which he did not.

Dependent claims 14-20 and 22-26 depend on independent claims 13 and 21, respectively, and therefore include all their limitations. Accordingly, for at least these reasons, claims 13-26 are separately patentable over *Golub*. Appellant respectfully requests reconsideration and that the rejection of 13 and 21 under 35 U.S.C. §103(a) be overturned.

C. Rejection of claims 16 and 24 Under 35 U.S.C. § 103 as Made Obvious by *Golub*

Claims 16 and 24 depend from claims 13 and 21, respectively, and incorporate the limitations of those claims. As discussed above in the traversal of claims 13 and 21 as being made obvious by *Golub*, the reference may not be relied on for the reasons articulated in section VII(B)(1-4) of this Appeal Brief. Thus, at least for these reasons, claims 16 and 24 are separately patentable in view of *Golub*.

Claims 16 and 24 are further separately patentable because *Golub* fails to teach or suggest the limitations of "the cytokine receptors . . . increased at least three-fold relative to non-contacted blood or a fraction thereof," as in claim 16, and "prior to the collecting, the number of cytokine receptors in the portion of the blood . . . increased by a least three-fold relative to the portion of the blood prior to the contacting with the therapeutic substance," as in claim 24. (App., claims 16, 24). As discussed previously, *Golub* only describes a method of enhancing endogenous ***cytokine IL-10 production*** in mammalian cells and tissues, which includes administering an effective amount of a tetracycline derivative. (Abstract). *Golub* is completely lacking in any such teaching or suggestion because *Golub* makes no mention whatsoever of cytokine receptors, let alone that cytokine receptors would increase at least three-fold upon contact with tetracycline or a tetracycline-like compound. Moreover, *Golub* contemplates ***tetracycline derivatives with little or no antimicrobial activity***. (col. 7, lns. 35-37; claim 2). Appellant's invention does not similarly include such a limitation, but only requires tetracycline or a tetracycline-like compound administered to blood or a fraction thereof. (App., claims 13,

21). Such a dramatic change in the property of a chemical, namely, a change in the level of microbial activity of the compound, would not necessarily result in the same effects when administered to blood.

Accordingly, for at least these reasons, claims 16 and 24 are separately patentable over *Golub*. Appellant respectfully requests reconsideration and that the rejection of claims 16 and 24 under 35 U.S.C. § 103(a) be overturned.

D. Rejection of claims 17 and 23 Under 35 U.S.C. § 103 as Made Obvious by *Golub*

Claims 17 and 23 depend from claims 13 and 21, respectively, and incorporate the limitations of those claims. As discussed above in the traversal of claims 13 and 21 as being made obvious by *Golub*, the reference may not be relied on for the reasons articulated in section VII(B)(1-4) of this Appeal Brief. Thus, at least for these reasons, claims 17 and 23 are separately patentable in view of *Golub*.

Claims 17 and 23 are further separately patentable because *Golub* fails to teach or suggest the limitations of "cytokine receptors . . . selected from the group consisting of interleukin-1 receptors and tumor necrosis factor receptors." (App., claims 17, 23). As discussed previously, *Golub* only describes a method of enhancing endogenous ***cytokine IL-10 production*** in mammalian cells and tissues, which includes administering an effective amount of a tetracycline derivative. (Abstract). *Golub* is completely lacking in any teaching or suggestion of claims 17 and 23 because *Golub* makes no mention whatsoever of cytokine receptors, let alone the specific cytokine receptors of interleukin-1 receptors and tumor necrosis factor receptors.

Accordingly, for at least these reasons, claims 17 and 23 are separately patentable over *Golub*. Appellant respectfully requests reconsideration and that the rejection of claims 17 and 23 under 35 U.S.C. § 103(a) be overturned.

E. Rejection of claims 19 and 25 Under 35 U.S.C. § 103 as Made Obvious by *Golub*

Claims 19 and 25 depend from claims 13 and 21, respectively, and incorporate the limitations of those claims. As discussed above in the traversal of claims 13 and 21 as being made obvious by *Golub*, the reference may not be relied on for the reasons articulated in section VII(B)(1-4) of this Appeal Brief. Thus, at least for these reasons, claims 19 and 25 are separately patentable in view of *Golub*.

Claims 19 and 25 are further separately patentable because *Golub* fails to teach or suggest the limitation of "wherein the blood or the fraction thereof includes a gamma-globulin fraction, a anti-hemophilia factor fraction, a albumin fraction, serum and plasma." (App., claims 19, 25). Representatively, according to the Application, processing the plasma into a gamma-globulin fraction, an anti-hemophilia factor fraction and an albumin fraction comprises one or more of the following procedures: (a) fractional precipitation with ammonium sulfate and similar salts; (b) organic solvent precipitation with cold ethanol or acetone and other such alcohols and ketones; (c) selective adsorption on calcium phosphate gels or with barium sulfate; (d) isoelectric precipitation by pH adjustment to the point at which there is no net charge on a given protein; and (e) chromatography by use of adsorbents such as CM- or DEAE-cellulose or by "Sephadex" gel filtration. Other procedures for selectively fractionating and purifying blood proteins involve the use of amino acids such as glycine and beta alanine, water-soluble organic polymers such as polyethylene glycol and polypropylene glycol, and water-insoluble polyelectrolyte polymers containing basic amino groups such as the dimethylaminopropylimide group. (App., p.24, ¶ [0306]).

The Examiner relies on a theory of inherency in rejecting these claims; however, the Examiner has not met his burden. Specifically, the Examiner states, "[u]pon centrifugation, blood is inherently separated into fractions containing globulin, anti-hemophilia factor, albumin, serum, and plasma." (Dec. 11 Final Office Action, p.3). In relying on a theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied art. *Ex parte Levy*, 17 USPQ.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Although centrifugation is noted in the Application for the recovery of serum and plasma from blood

(App., p.23, ¶ [0303]), centrifugation is decidedly absent from any of the processes describing the further fractionation of plasma into a gamma-globulin fraction, an anti-hemophilia factor fraction and an albumin fraction. (App., p.24, ¶ [0306]). In fact, the only processes disclosed in the Application for processing the plasma into a gamma-globulin fraction, an anti-hemophilia factor fraction and an albumin fraction are (a) fractional precipitation with ammonium sulfate and similar salts; (b) organic solvent precipitation with cold ethanol or acetone and other such alcohols and ketones; (c) selective adsorption on calcium phosphate gels or with barium sulfate; (d) isoelectric precipitation by pH adjustment to the point at which there is no net charge on a given protein; and (e) chromatography by use of adsorbents such as CM- or DEAE-cellulose or by "Sephadex" gel filtration. Other procedures for selectively fractionating and purifying blood proteins involve the use of amino acids such as glycine and beta alanine, water-soluble organic polymers such as polyethylene glycol and polypropylene glycol, and water-insoluble polyelectrolyte polymers containing basic amino groups such as the dimethylaminopropylimide group. (*Id.*). Thus, the Examiner has failed to meet his burden in rejecting claims 19 and 25.

Accordingly, for at least these reasons, claims 19 and 25 are separately patentable over *Golub*. Appellant respectfully requests reconsideration and that the rejection of claims 19 and 25 under 35 U.S.C. § 103(a) be overturned.

F. Rejection of claims 20 and 26 Under 35 U.S.C. § 103 as Made Obvious by *Golub*

Claims 20 and 26 depend from claims 13 and 21, respectively, and incorporate the limitations of those claims. As discussed above in the traversal of claims 13 and 21 as being made obvious by *Golub*, the reference may not be relied on for the reasons articulated in section VII(B)(1-4) of this Appeal Brief. Thus, at least for these reasons, claims 20 and 26 are separately patentable in view of *Golub*.

Claims 20 and 26 are further separately patentable because *Golub* fails to teach or suggest the limitations of "further comprising administering the composition," as in claim 20, and "further comprising administering the blood or fraction thereof," as in claim 26, to treat a disease, condition or disorder. (App., claims 20, 26). For process claims, statements in a preamble reciting the purpose or intended use of the claimed invention must be evaluated to

determine whether the recited purpose or intended use results in a manipulative difference. MPEP § 2111.02. In the case of claims 20 and 26, the manipulative difference is that ***a composition, blood or fraction thereof*** is being administered, rather than a direct injection of tetracycline or a tetracycline-like compound. (App., claims 20, 26). Representatively, the composition, blood or fraction thereof can be administered intravenously, intraperitoneally or intracardially. (App., p.11, ¶ [0157]; p.43, ¶ [0566]). *Golub*, on the other hand, only contemplates ***direct injection*** of a non-antibacterial tetracycline derivative:

> The invention is a method of enhancing endogenous interleukin-10 production in mammalian cells and tissues, which includes administering an effective amount of a tetracycline derivative. The method also includes enhancing interleukin-10 production by administering an effective amount of the tetracycline derivative to a mammal. Preferred tetracycline compounds are tetracycline compounds which have been modified to reduce or eliminate their antimicrobial activity.

(Abstract). Thus, the manipulative difference is that tetracycline or a tetracycline-like compound is first contacted with a blood product and refined to a composition that can then be administered to treat a disease, condition or disorder. (App., claims 20, 26).

Accordingly, for at least these reasons, claims 20 and 26 are separately patentable over *Golub*. Appellant respectfully requests reconsideration and that the rejection of claims 20 and 26 under 35 U.S.C. § 103(a) be overturned.

VIII. CONCLUSION AND RELIEF

Accordingly, it is submitted that the rejections of claims 13-26 based on 35 U.S.C. § 103 be overturned.

Respectfully submitted,

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CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being submitted electronically via EFS Web to the United States Patent and Trademark Office on January 31, 2007.

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Si Vuong

IX. CLAIMS APPENDIX

The claims involved in this Appeal are as follows:

1-12. Cancelled.

13. (Previously Presented) A process, comprising:

contacting blood or a fraction thereof with a therapeutic substance selected from at least one of tetracyclines and tetracycline-like compounds thereby increasing the level of cytokine receptors in the blood or the fraction thereof; and

after the contacting, isolating the blood or the fraction thereof having the increased cytokine receptors thereby producing a composition suitable for administration for the treatment of a disease, condition or disorder.

14. (Previously Presented) The process of claim 13, wherein the contacting is *in vivo*.

15. (Previously Presented) The process of claim 13, wherein the contacting is *in vitro*.

16. (Previously Presented) The process of claim 13, wherein the cytokine receptors are increased at least three-fold relative to non-contacted blood or a fraction thereof.

17. (Previously Presented) The process of claim 13, wherein the cytokine receptors are selected from the group consisting of interleukin-1 receptors and tumor necrosis factor receptors.

18. (Previously Presented) The process of claim 13, further comprising processing the isolated blood or the fraction thereof by a process selected from the group consisting of: centrifugation, filtration, fractional precipitation, organic solvent precipitation, selective absorption, isoelectric precipitation, and chromatography.

19. (Previously Presented) The process of claim 18, wherein the blood or the fraction thereof includes a gamma-globulin fraction, a anti-hemophilia factor fraction, a albumin fraction, serum and plasma.

20. (Previously Presented) The process of claim 13, further comprising administering the composition to treat a disease, condition or disorder wherein the disease, condition or disorder is one of viral hemorrhagic diseases, sepsis, cachexia, rheumatoid arthritis, acute

cardiovascular events, chronic myelogenous leukemia, transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis, systemic inflammatory response syndrome, adult respiratory distress syndrome, acute liver failure, inflammatory bowel disease and Crohn's disease.

21. (Previously Presented) A process, comprising:

contacting blood *in vivo* with a therapeutic substance selected from at least one of tetracyclines and tetracycline-like compounds thereby increasing the level of cytokine receptors in the blood;

after the contacting, collecting a portion of the blood; and

after the collecting, processing the portion of the blood to isolate a blood fraction comprising cytokine receptors.

22. (Previously Presented) The process of claim 21, wherein the processing is selected from the group consisting of: centrifugation, filtration, fractional precipitation, organic solvent precipitation, selective absorption, isoelectric precipitation and chromatography.

23. (Previously Presented) The process of claim 21, wherein the cytokine receptors are selected from the group consisting of interleukin-1 receptors and tumor necrosis factor receptors.

24. (Previously Presented) The process of claim 21, wherein prior to the collecting, the number of cytokine receptors in the portion of the blood is increased by a least three-fold relative to the portion of the blood prior to the contacting with the therapeutic substance.

25. (Previously Presented) The process of claim 21, wherein the blood or the fraction thereof includes a gamma-globulin fraction, a anti-hemophilia factor fraction, a albumin fraction, serum and plasma.

26. (Previously Presented) The process of claim 21, further comprising administering the blood or fraction thereof to treat a disease, condition or disorder wherein the disease, condition or disorder is one of viral hemorrhagic diseases, sepsis, cachexia, rheumatoid arthritis, acute cardiovascular events, chronic myelogenous leukemia, transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid

inflammation, autoimmune disorders, multiple sclerosis, systemic inflammatory response syndrome, adult respiratory distress syndrome, acute liver failure, inflammatory bowel disease and Crohn's disease.

X. EVIDENCE APPENDIX

Not Applicable.

XI. RELATED PROCEEDINGS APPENDIX

Not Applicable.